III. REMARKS

The specification has been amended to incorporate Applicant's priority claim.

Claim 1 has been amended to address a minor informality, and not for a reason related to patentability. Therefore, the present amendment has no further limiting effect on the scope of the claims.

No new matter has been added to the present application by the amendment.

A. The Invention

The present invention pertains broadly to a "method for the production of heterologous proteinaceous substances in plant material" such as "obtain[s] secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17. Various other embodiments, in accordance with the claimed invention, are recited by the dependent claims.

The present invention provides a method for producing heterologous proteinaceous substances in plant material, whether protonema moss tissue or protonema liverwort tissue, wherein the proteinaceous substances produced by the transformed protonema tissue are advantageously secreted and obtained without disrupting producing tissues or cells. Persons skilled in the art would recognize that the present invention advantageously utilizes protonema tissue, wherein "protonema" is defined in the art as "the usually filamentous thalloid stage of the gametophyte in mosses and in some liverworts comparable to the prothallium in ferns" (See Webster's new collegiate dictionary, 1977, p. 927)(of record). The novelty of the present invention over the prior art relates to the step of "obtaining secreted heterologous proteinaceous substances...without disrupting producing tissues or cells" because persons skilled in the art

would not have predicted that secreted proteinaceous substances could be obtained from the culture media of transformed protonema tissue, i.e., mature plant tissue having cell walls, without disrupting the producing tissues or cells.

In particular, persons of ordinary skill in the art would not have predicted that transformed protonema tissue, i.e., mature plant tissue having cell walls, would secrete heterologous proteinaceous substances into cell culture medium so that the secreted heterologous proteinaceous substances can be obtained without disrupting producing tissues or cells. (c.f., e.g., U.S. Patent 6,096,546 issued to Raskin, hereafter the "Raskin Patent," of record, and U.S. Patent No. 6,020,169 issued to Lee et al., of record).

B. The Rejections

Claims 1-3 and 17 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Reutter (K. Reutter et. al., PLANT TISSUE CULTURE AND BIOTECHNOL. 2:142-147, 1996, hereinafter the "Reutter Article") in view of Lee et al. (U.S. Patent No. 6,020,169, hereafter the "Lee Patent").

Claims 1-3 and 17 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the Reutter Article in view of the Lee Patent, and in further view of Nasu et al. (M. Nasu et al., 84 J. FERM. BIOENG. 519: 519-523 (1997), hereafter, the "Nasu Article").

Applicants respectfully traverse the rejection and request reconsideration of the above-captioned application for the following reasons.

C. APPLICANTS' ARGUMENTS

The basic argument with respect to why the Examiner's Section 103 rejection is untenable and must be withdrawn is as follows. The Examiner starts from the Reutter Article,

which describes the cultivation of transformed moss protonema and the production of heterologous proteins inside (i.e., intracellularly) this tissue. That is the end of the scope of the Reutter Article. Up to now Applicants have concerned themselves with showing the Examiner, in great detail, how those skilled in the art could approach the object to be achieved by the present invention in view of the Reutter Article. They would search for publications on the secretory production of heterologous proteins in moss systems, but find nothing. Because persons skilled in the art would also not have found any publications regarding other comparable systems of intact lower plants, they might be inclined to look for publications on the use of systems that relate to intact higher plants. Then the persons skilled in the art would have found the documents cited by the Examiner and by Applicants. A person of ordinary skill in the art would have recognized that the combined disclosures of the prior art (e.g., Raskin and Lee) only relates to the destruction of the producing tissue of intact plants, or else to the special cases of rhizosecretion and guttation, which are not transferable to moss protonema in view of the lack of roots or vascular systems. This has already been acknowledged by the Examiner and these objections based on the prior art have been withdrawn.

The above facts shows clearly that those skilled in the art in the field of intact plant organisms cannot obtain any stimulus and/or motivation leading to the solution according to the present invention. In addition, some of the publications in the prior art describe precisely which expression systems offer which advantages and disadvantages. In this regard, Applicants have already shown, in particular with reference to the Lee Patent and the Raskin Patent, that those skilled in the art must assume in complete plant organisms that a heterologous protein – even with a suitable signal sequence – travels only into the space between the cell membrane and the cell wall (i.e., the apoplastic space, or the "APO space"). In complete plant organisms, a heterologous protein – even with a suitable signal sequence – travels to, but does not pass

through, the cell wall of a mature plant organism, as is surprisingly the case according to the present invention.

i. The Section 103 Rejection

A prima facie case of obviousness requires a showing that the scope and content of the prior art teaches each and every element of the claimed invention, and that the prior art provides some teaching, suggestion or motivation, or other legitimate reason, for combining the references in the manner claimed. KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 1739-41 (2007); In re Oetiker, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). Furthermore, a proper rejection under Section 103 requires showing (1) that a person of ordinary skill in the art would have had a legitimate reason to attempt to make the composition or device, or to carry out the claimed process, and (2) that the person of ordinary skill in the art would have had a reasonable expectation of success in doing so. PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007).

In this case, none of the cited references teach, or even suggest, obtaining secreted heterologous proteinaceous substances from intact protonema tissue, which is made up of cells having cell walls. Therefore, the combination of the Reutter Article, the Lee Patent and the Nasu Article fails to teach, or suggest, "obtaining secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells…wherein the plant material is protonema tissue" as recited by independent claims 1 and 17. Furthermore, the Examiner has failed to establish both legitimate reason for combining the disclosures of the Reutter Article and the Lee Patent and that a person of ordinary skill in the art would have a reasonable expectation of success of arriving at Applicants' claimed invention even assuming the combination of Reutter, Lee and Nasu is properly justified (which is not a valid assumption).

ii. The Reutter Article

The Reutter Article discloses the transformation of moss protoplasts, in particular *Physcomitrella patens* protoplasts (Reutter Article, page 143, line 4, to page 144, line 5). The Reutter Article also discloses culturing protonema (Reutter Article, at 145, lines 1-5). However, the Reutter article is completely silent with respect to obtaining the intracellular expressed heterologous protein without disrupting producing tissues or cells as recited in claims 1 and 17. It can be inferred from the Reutter Article that any detected material was from lysed or disrupted cells. The purpose of Reutter's study was not to obtain secreted heterologous proteinaceous substances from culture media and there is no indication in their study that this was achieved or even possible (Declaration Under 37 C.F.R. § 1.132 by Ralph Reski, of record, hereafter the "Reski Declaration," at ¶¶ 44 and 46).

Thus, there is no teaching in Reutter that isolation of secreted heterologous proteinaceous substances from medium was possible.

Dr. Reski testifies that, as co-author of the Reutter Article, he knows that stably transformed *Physcomitrella* protonema of the Reutter article expressed a heterologous protein that was localized in the cells (Reski Declaration, at ¶ 46). Dr. Reski testified, as co-author of the Reutter Article, that no secretion of the heterologous protein into the medium was observed from stably transformed protonema. Consequently, the Reutter Article neither teaches, nor suggests, there would be secretion of heterologous protein through the cell wall of protonema cells.

In view of the above, it is a fact that the Reutter Article does not disclose or suggest the steps of (a) "culturing...transformed...protonema tissue;" and (b) "obtaining secreted

heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17.

For all of these reasons, the Reutter Article cannot support any rejection of the claims under § 103.

iii. The Lee Patent

The Lee Patent describes the isolation of a heterologous protein from suspension of cultured tobacco cells (col. 12, lines 6-9 and 48-49). However, it is known that single-cell cultures of tobacco cells are permeable to proteins at least as large as 150 kDa (see Raskin, U.S. Patent 6,096,546, of record, hereafter the "Raskin Patent," at col. 2, lines 5-10). Lee estimates the size limit to be about 50 kDa or higher (col. 6, line 29). Thus, Lee does nothing to show the obviousness of the surprising and unexpected result of the present invention, namely obtaining secreted proteins from the media of cultured protonema, which is photosynthetically active and differentiated tissue having cell walls.

The Lee Article does not teach, or suggest, that transformed protonema secrete heterologous protein. Therefore, the Lee Patent does not disclose or suggest either of the steps of (a) "culturing...transformed...protonema tissue;" and (b) "obtaining secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17. In fact, none of the prior art documents show secretion of heterologous proteins through the cell wall of photosynthetically active tissue of a plant without disruption of the cell wall.

iv. The Nasu Article

The Nasu Article pertains to the transformation of *Marchantia polymorpha* that is a haploid liverwort with very small genome DNA (See Abstract). In particular, the Nasu Article discloses transforming single *Marchantia* cells (Nasu article, at 520, first column, lines 1-11). Thus, the Nasu Article pertains to cultures of single cells, and not to intact plant tissue. The transformed cells were subsequently fixed in formaldehyde, which a person of ordinary skill in the art would realize kills the cells, and then the dead cells were subjected to an assay in order to prove intracellular expression of the heterologous proteins (Nasu Article, at 520, first column, lines 35-47, and see Figure 4).

The above analysis of the Nasu Article is supported by the testimony of Dr. Gorr, who states that the Nasu Article does not teach that heterologous protein produced by transformed *Marchantia* cells would be secreted through the cell walls of mature protonema cells (See Declaration Under 37 C.F.R. § 1.132 by Gilbert Gorr, of record, hereafter the "Gorr Declaration,", ¶ 28). Dr. Reski also testified that the Nasu Article does not teach, or suggest, the application of a signal peptide, and therefore, also neither teaches, nor suggests, there would be secretion of heterologous protein through the cell wall of protonema cells (Reski Declaration, ¶ 46). Thus, the Nasu article plainly does not teach or suggest either of the steps, in accordance with claims 1 and 17 of the present invention, of (a) "culturing...transformed...protonema tissue;" and (b) "obtaining secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17.

For all of these reasons, Nasu cannot support any rejection of the claims under § 103.

v. Summary of the Disclosures

In view of the above, neither the Reutter Article, the Lee Patent, nor the Nasu Article, either alone or in combination, teach or even suggest (a) "culturing...transformed...protonema tissue;" and (b) "obtaining secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17. Furthermore, no combination of the Reutter Article, the Lee Patent and the Nasu Article teaches or suggests "culturing, in a culture medium, photosynthetically-active plant material transformed with a construct encoding a signal peptide operably linked to a protein" as recited by claim 17.

For all of the above reasons the Examiner has failed to establish a prima facie case of obviousness against independent claims 1 and 17 of the above-captioned application.

vi. Lack of a Legitimate Reason to Combine Disclosures

A proper rejection under Section 103 requires showing (1) that a person of ordinary skill in the art would have had a legitimate reason to attempt to carry out the claimed process, and (2) that the person of ordinary skill in the art would have had a reasonable expectation of success in doing so. PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007). In this case, the Examiner has failed to establish a legitimate reason for combining the disclosures of the Reutter Article, the Lee Patent and the Nasu Article for the following reasons.

The Reutter Article is limited to teaching a method for stably transforming moss protoplasts so as to produce intracellular heterologous protein; however, the reference does not teach, or suggest, how to obtain secreted heterologous protein from mature protonema without disrupting producing tissues or cells (See, e.g., Gorr Declaration, ¶ 30; Reski Declaration. ¶ 49). There is also no prior art teaching with respect to the secretory production of heterologous proteins in moss systems or other comparable lower plant systems.

The Lee Patent discloses isolation of a biologically active heterologous protein from single tobacco cells held in suspension culture. Tobacco is a higher plant (i.e., a dicot) as recognized by the Lee Patent, which states "[t]he term 'plant; encompasses any higher plant and progeny thereof, including monocots (e.g., rice), dicots (e.g., tobacco, Arabidopsis, carrot, etc.), gymnosperms, etc." (col. 8, lines 49-51). Mosses and liverworts do not belong to the higher plants that have vascular systems and, therefore, the two are not comparable and the combination of Lee with Reutter is inappropriate as would be understood by a person of ordinary skill in the art.

More specifically, mosses and liverworts do not belong to the higher plants such as, *e.g.*, tobacco and Arabidopsis, and the difference between the biology of mosses and higher plants is well recognized in the art (See. e.g., D. Schaefer et al., *Stable Transformation of the Moss Physcomitrella Patens*, 226 MOL. GEN. GENET. 418, 418 (1991), of record). Even different types of single cells held in culture cannot easily be compared with one another, much less compared to multicellular protonema in culture, as far as their properties and in particular their cell wall morphology are concerned. In this context, additional reference is made to another publication of the inventor, Dr. Reski, stating that

> "[o]ne of the problems when working with mosses is their rigid cell wall, which impedes digestion with any other enzyme combination than Driselase." S. Rother et al., *Fate of a Mutant Macrochloroplast in Somatic Hybrids*, 143 J. PLANT PHYSIOL. 72, 75 (1994)(emphasis added).

These are facts that would be known by a person of ordinary skill in the art. In view of these facts, a person of ordinary skill in the art would not expect the cell walls of moss and liverwort protonema to necessarily behave in the same manner as the cell wall of tobacco cells in suspension.

In other words, comparing mosses and liverworts (lower non-flowering plants lacking a root structure and vascular system) to higher order plants (flowering plants having roots and a vascular system) is less useful than comparing apples and oranges because apples and oranges are at least both higher order plants. A person of ordinary skill in the art would not look to the higher order plant systems for subject matter that would be applicable to lower order plants, such as mosses and liverworts. For this reason alone, the Examiner has failed to establish a legitimate reason for combining the Lee Patent (higher order plants) with the Reutter Article (lower order plants). In other words, a person of ordinary skill in the art would understand that, in view of the technology employed by the present invention, the Lee Patent is non-analogous art because Lee employs single cells and the Reutter Article employs intact plant organisms. Furthermore, the Lee Patent is non-analogous art because it pertains to undifferentiated or dedifferentiated single cells, whereas the Reutter Article pertains to intact mature plant organisms.

However, these are not the only reasons the Examiner has failed to establish a legitimate reason for combining the disclosure of the Lee Patent with that of the Reutter Article. It was known in the art that complete plant organisms, transformed to produce heterologous protein (even when transformed to include a suitable signal sequence), fail to secrete the heterologous protein beyond the apoplastic space (i.e., the space between the plasma membrane and the cell wall). See, e.g., the Raskin Patent and the Lee Patent.

Furthermore, the Lee Patent actually teaches away from the combination made by the Examiner. Lee explicitly states that

> "[p]lant suspension culture systems provide significant advantages over protein production in intact transgenic plants, which requires cultivation, harvesting and expensive extraction procedures to obtain non-secreted foreign proteins" (col. 4, lines 34-38, emphasis added).

Lee uses single cells. However, the claimed invention relates to "intact transgenic plants," which according to the Lee Patent are not expected to secrete heterologous protein. A person of ordinary skill in the art would immediately understand from the disclosure of Lee that higher order plant cell suspension culture is used to overcome the need to destroy plant tissue in order to extract non-secreted heterologous proteins from transgenic plants of lower order. Therefore, a person of ordinary skill in the art would have no legitimate reason to apply Lee's method (which pertains to single cell suspension) to intact transgenic plants of Reutter, which are not expected to secrete heterologous protein into the culture media.

According to the Examiner, Lee describes the isolation of a heterologous protein from individual tobacco cells. These individual cells may be permeable even for large proteins. Lee is, however, not capable of suggesting the present invention, precisely because the explicit teaching above that intact plants would require "extensive extraction procedures" to obtain heterologous proteins. The Examiner does not find this argument convincing because the Raskin Patent allegedly asserts that the cell walls are permeable due to the presence of a secretion signal at the protein. According to her, secretion is a function of these signals that holds true not only for tobacco cells but also for other types of plant cells. However, the Examiner has not taken into account the difference between the systems being compared. It is true that these signal sequences may initiate the secretory pathway in single tobacco cells, but Applicants have already shown in detail that secretion through the cell wall in intact plants has not been shown anywhere in the prior art. The Examiner ignores this inconvenient fact. Applicants file herewith a copy of Shinya Matsumoto et al., *Characterization of a Human Glycoprotein (Erythropoietin) Produced in Cultured Tobacco Cells*, 27 PLANT MOLECULAR BIOLOGY 1163-1172 (1995), hereafter the "Matsumoto Article," a copy of which is filed herewith), which stands for the proposition that the presence of a signal peptide does not guarantee the secretion of the heterologous protein

through the cell wall of tobacco cells (See, e.g., Matsumoto Article, at 1169, col. 2, line 19, to 1170, col. 1, line 8). In view of the above, the fact that Applicants' claimed invention achieves the secretion of heterologous protein into the culture medium of intact whole plants (protonema), is an unexpected result that is not predicted by the prior art.

The Nasu Article discloses the transformation of the liverwort *Marchantia polymorpha*, which does not employ a signal peptide and which employs a technique of killing and staining transformed cells to detect intracellular foreign protein. The Nasu Article makes up none of the deficiencies of the Reutter Article and the Lee Patent with respect to the lack of a legitimate reason to combine references.

For all of the above additional reasons, the Examiner has failed to establish a prima facie case of obviousness against the claimed invention because the Examiner has no legitimate reason to combine the Reutter Article with the Lee Patent and the Nasu Article.

vii. No Reasonable Expectation of Success

A proper rejection under Section 103 requires showing (1) that a person of ordinary skill in the art would have had a legitimate reason to attempt to carry out the claimed process, and (2) that the person of ordinary skill in the art would have had a reasonable expectation of success in doing so. PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007). In this case, the Examiner has failed to establish a legitimate reason for combining the disclosures of the Reutter Article, the Lee Patent and the Nasu Article for the following reasons.

A person of ordinary skill in the art would understand that proteins penetrating the cell membrane of an intact mature plant cell may still be contained by the cell wall, which may serve as a barrier to secretion of protein into cell culture medium (See, e.g., Matsumoto Article, at 1169, col. 2, line 19, to 1170, col. 1, line 8). A person of ordinary skill in the art would also

know that the space between the cell wall and the cell membrane of an intact, mature plant cell is known as the "apoplastic space."

In view of the above facts, a person of ordinary skill in the art would have no reason to expect the subject matter disclosed by the Lee Patent to change the fact that transformed *Physcomitrella patens* protonema (such as the Examiner contends may be derived from protoplasts of the Reutter Article) are not expected to secrete heterologous proteinaceous substances into the culture medium. It is a fact that the method of the Reutter Article did not employ a signal peptide, that heterologous protein was localized in the cells, and that no secretion of the heterologous protein into the medium was observed from stably transformed protonema (Reski Declaration, at ¶¶ 44 and 46). Therefore, it is a fact that the transformed cells of Reutter are not expected to secrete heterologous protein.

It is also a fact that the Lee Patent states

> "[p]lant suspension culture systems provide significant advantages over protein production in intact transgenic plants, which requires cultivation, harvesting and expensive extraction procedures to obtain non-secreted foreign proteins" (col. 4, lines 34-38, emphasis added).

Thus, even the Lee Patent discloses that one should not expect "intact transgenic plants," such as the "protonema tissue" recited by claims 1 and 17 of the present invention, to secrete heterologous protein. A person of ordinary skill in the art would immediately understand from the combined disclosures of the Reutter Article and the Lee Patent that transformed "protonema tissue" is not expected to secrete the heterologous protein beyond the rigid cell wall, see supra page 13, and into the culture medium. The disclosure of the Lee Patent is limited to using single cell suspensions of higher plants (and not protenema of lower plants) to overcome the need to destroy transformed plant tissue in order to extract non-secreted heterologous proteins from intact transgenic plants of lower order. Therefore, a person of ordinary skill in the art would

have **no reason** to expect that by applying Lee's method (which pertains to single cell suspensions of higher plants) to intact transgenic plants of lower order of Reutter, the result would be transformed protonema tissue that secretes heterologous protein into the culture media so that "secreted heterologous proteinaceous substances [are obtained] from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17.

The Nasu Article discloses the transformation of the liverwort *Marchantia polymorpha*, which does not employ a signal peptide and which employs a technique of killing and staining transformed cells to detect intracellular foreign protein. Therefore, it is a fact that the transformed cells of Nasu are not expected to secrete heterologous protein (Reski Declaration, ¶ 46). The Nasu Article does not change the fact that a person of ordinary skill in the art would have no reasonable expectation of success of arriving at Applicants' claimed invention even assuming, *arguendo*, there exists a legitimate reason to combine the Reutter Article and the Lee Patent (which, of course, is an invalid assumption).

In view of the above facts, the Examiner has failed to establish a prima facie case of obviousness against the claimed invention because the Examiner has failed to demonstrate that the combination of the Reutter Article with the Lee Patent and the Nasu Article would have a reasonable expectation of success with respect to creating intact transgenic protonema that secrete a foreign protein into the culture media. On the contrary, the combination of the disclosures of the Reutter Article, the Lee Patent and the Nasu Article would lead a person of ordinary skill in the art to conclude that transformed "protonema tissue" would not secrete the heterologous protein into the culture medium so that there would be no expectation that the combination would be able to "[obtain] secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17. These expectations are in agreement with the knowledge in the art regarding the

possibility of producing heterologous proteins in intact plants; namely, that with the exception of certain exceptions that are not relevant here, e.g., rhizosecretion and guttation, intact plants must be broken up or destroyed in order to obtain heterologous proteins (See citations, supra, to the Raskin and Lee Patents).

The Examiner has also failed to appreciate the fact that use of a signal peptide does not guarantee that heterologous protein will pass through the cell wall of even individual plant cells (See, e.g., Matsumoto, at 1169, col. 2, line 19, to 1170, col. 1, line 8). In view of the above facts, the Examiner cannot establish *a priori* that a person of ordinary skill in the art would have had a reasonable expectation that the combination of Reutter and Lee would succeed at arriving at Applicants' claimed invention wherein intact transgenic plants (protonema) secrete heterologous protein into the plant culturing media.

For all of the above reasons, the Examiner has failed to establish a prima facie case of obviousness against the claimed invention because the Examiner has not established a reasonable expectation of success of arriving at the claimed invention even if the combination of the Reutter Article with the Lee Patent and the Nasu Article is justified (which it is not).

viii. Indicia of Non-obviousness (Unexpected Results)

A patentability analysis under 35 U.S.C. § 103 requires (a) determining the scope and content of the prior art, (b) ascertaining the differences between the prior art and the claimed subject matter, (c) resolving the level of ordinary skill in the pertinent art, and (d) considering secondary considerations that may serve as indicia of nonobviousness or obviousness. Graham v. John Deere Co. of Kansas City, 148 U.S.P.Q. 459, 467 (1966). Secondary considerations of non-obviousness include commercial success, long felt but unsolved needs, and failure of others. Id.

In this case, WO 97/04122, a copy of which is filed herewith, and which corresponds to International Patent Application No. PCT/US96/12025, filed July 19, 1996 (and which correspond to the Lee Patent), states at 5, lines 2-4, that

> "[p]lant suspension culture systems provide significant advantages over protein production in intact transgenic plants, which requires cultivation, harvesting and expensive extraction procedures to obtain non-secreted foreign proteins" (emphasis added).

Thus, a need was felt since at least July 19, 1996 for a system of intact transgenic plants that could be cultivated without having to employ harvesting and expensive extraction procedures in order to obtain foreign proteins that are generally not secreted from the intact transgenic plants. The Lee Patent and WO 97/04122 acknowledges the inability of intact transgenic plants to secrete heterologous protein. The Lee Patent circumvents this disadvantage encountered with intact transgenic plants by using cell suspensions of transformed higher order plants. The present invention, however, achieves what was previously thought impossible, which according to Lee is to create intact transgenic plants that can secrete heterologous protein in substantial amounts into the culture media. The present invention was initially filed on October 1, 1999 as German Patent Application No. 19947290.4. Therefore, it was over three years before the long felt need acknowledged by Lee would be satisfied by the present invention.

In view of the fact that Applicants' claimed invention satisfies the long felt need for intact transgenic plants that can secrete heterologous protein in substantial amounts, Applicants' unexpected achievement should be sufficient to overcome the alleged prima facie case assuming one had been properly made (which is an invalid assumption).

Furthermore, Applicants' claimed invention achieves success where the prior art has not, which is further evidence of the non-obviousness of the present invention.

viii. Specific Comments Regarding Examiner's Contentions

The Examiner states at 4, lines 11-19, of the Office Action dated September 24, 2007, that

> "Applicant urges that Lee teaches away from the combination because it touts the advantages of suspension cell culture and the instant claims are drawn to intact plants; one of ordinary skill in the art would have to assume that intact plants could not secrete into the media....
>
> This is not found persuasive. Lee touts the advantages of suspension cell culture because of the difficulty of growing most whole plant in liquid media; it has nothing whatsoever to do with an assumption that intact plants could not secrete into the media. One of skill in the art of transforming and growing mosses and liverworts would know that growing protonema in liquid culture is very possible, as shown by Reutter" (emphasis added).

The Examiner has plainly misconstrued the disclosure of the Lee Patent, at col. 4, lines 34-38, which states that

> "[p]lant suspension culture systems provide significant advantages over protein production in intact transgenic plants, which requires cultivation, harvesting and expensive extraction procedures to obtain non-secreted foreign proteins" (emphasis added).

A person of ordinary skill in the art would instantly understand from this passage from Lee that intact transgenic plants do not secrete foreign proteins so that expensive extraction procedures are needed to obtain the foreign proteins from the transformed plants. Whether cultivation and harvesting steps are also required is immaterial to the fact that the Lee Patent discloses that intact transgenic plants do not secrete heterologous protein!

To the extent that the Examiner has ignored Lee's teaching that intact transgenic plants are plagued by the disadvantage that foreign proteins are not secreted and therefore must be extracted, Applicants object. The Examiner is obligated to give a fair reading to what the Lee Patent teaches as a whole. See, e.g., In re Gordon, 221 U.S.P.Q. 1125, 1126 (Fed. Cir. 1984). In

this case, the Examiner has misconstrued the Lee Patent because a fair reading of this patent includes the fact that intact transgenic plants are not expected to secrete foreign proteins.

For all of the above reasons, the combination of Reutter with Lee, with or without the Nasu Article, is untenable against the present claims, and Applicants respectfully request reconsideration and withdrawal of the rejections under § 103.

IV. CONCLUSION

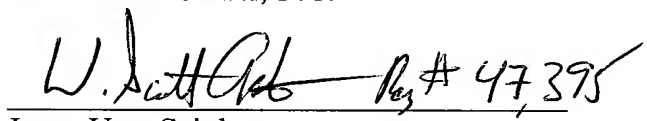
The Examiner has failed to establish a prima facie case of obviousness against independent claims 1 and 17 because neither the Reutter Article, the Lee Patent, nor the Nasu Article, either alone or in combination, teach or suggest (a) "culturing...transformed... protonema tissue;" and (b) "obtaining secreted heterologous proteinaceous substances from the culture medium without disrupting producing tissues or cells" as recited by independent claims 1 and 17. Furthermore, the Examiner's Section 103 rejection is untenable and must be withdrawn because the Examiner has failed to demonstrate a legitimate reason for combining the disclosures of Reutter, Lee and Nasu, and because the Examiner has failed to demonstrate that a person of ordinary skill in the art would have enjoyed a reasonable expectation of success of achieving the claimed invention if the proposed combination was made.

In addition, the Examiner has failed to consider Applicants' indicia of non-obviousness pertaining to solving a long felt but unsolved need and to achieving success when the prior art predicted failure.

For all of the above reasons, claims 1-3 and 17 are in condition for allowance, and a prompt notice of allowance is earnestly solicited.

Questions are welcomed by the below-signed attorney for Applicants.

Respectfully submitted,
GRIFFIN & SZIPL, P.C.



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